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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/334,969	06/17/1999	BENT KARSTEN JAKOBSEN	102286.410	5926

7590 06/30/2005

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 06/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/334,969	JAKOBSEN ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,14-27 and 34-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,14-27 and 34-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/25/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: pages 2 & 80 of clean copy of substitute specification filed 7/25/03 and pages 93, 105 and last page of marked-up copy of substitute specification filed 7/25/03.

DETAILED ACTION

1. Applicant's amendment filed 4/15/05 is acknowledged and has been entered.

2. Applicant is reminded of Applicant's election without traverse of Group I (claims 1-27), and species of the specific complex of a TCR tetramer comprising four αβ dimers and the specific linker molecule of avidin in Paper No. 7.

Claims 1-11, 14-27 and 34-36 read on the elected species and are presently being examined.

3. The disclosure is objected to because of the following informality:

There is a spelling error on page 93 of Appendix B filed 7/25/03 (marked-up copy of the substitute specification) and on page 80 of Appendix A filed 7/25/03 (the clean copy of the substitute specification), i.e., "R frenc s". There is also typographical error on page 2 of the clean copy of the substitute specification, i.e., "G n ral Background f th Inv ntion". In addition, irrelevant information appears on page 105 of Appendix B, i.e., a header and 5i, and there appears to be extra page at 106 in Appendix B that is a "document comparison done by Deltaview".

Applicant's statement in the said amendment filed 4/15/05 that the above listed pages have no errors is noted by the Examiner.

However, the above errors do appear in the clean copy of the substitute specification and the marked-up copy of the substitute specification, and copies of those pages are attached hereto.

Appropriate correction is required.

In view of Applicant's amendment filed 4/15/05, the following grounds of rejection remain.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103□ and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-11, 14-18, 26, 27 and 34-36 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/35991 (Applicant's IDS reference in the Form 1449 filed 1/31/00) in view of Golden et al (J. Immunol. Meth. Vol. 206: 163-169, 1997, Applicant's IDS reference in the Form 1449 filed 11/5/99), O'Shea et al (Science, Vol. 245: 646-648, 1989, Applicant's IDS reference in the Form 1449 filed 11/5/99), Garboczi et al (J. Immunology, Volume 157: 5403-5410, 1996, Applicant's IDS reference in the Form 1449 filed 11/5/99) and Schatz (Biotechnology, 11, 1993, pages 1138-1143, Applicant's IDS reference in the Form 1449 filed 11/5/99).

WO 97/35991 teaches soluble (i.e., extracellular domains) recombinant divalent and multivalent analogs (including tetravalent, i.e., a tetramer) of heterodimeric proteins and pharmaceutical compositions thereof, including αβ TCR that possess enhanced affinity for their target molecules, said αβ TCRs being associated via Ig linker molecules which may further comprise a toxin, i.e., a "cytotoxic agent" as recited in instant claim 26, and/or may be further linked by association via avidin (especially page 8, line 31, page 9, lines 1-4, page 10, lines 27-31, page 11, lines 1-7, page 14, lines 7-16, Figure 1D and legend, claims 1-5, 8, 10-14, 17, 27 and 28, page 1, lines 14-17, page 16, lines 1-14). With regard to instant claim 17, the recitation of a method wherein the claimed product is made carries no patentable weight in these product claims. In addition, WO 97/35991 teaches that the multimeric soluble TCR complexes may be useful in defining the specific peptide/MHC ligands recognized by uncharacterized tumor-specific T cells and T cells involved in autoimmune responses (especially page 10, lines 27-31 and page 11, line 1). WO 97/35991 also teaches production of the multimers in baculovirus with a yield of about 1 ug/ml (i.e., about 1 mg/L). WO 97/35991 also teaches short flexible Gly-Ser spacers between the TCR chain and the Ig portion (Figure 1D and legend).

WO 97/35991 does not teach multivalent soluble αβ TCR wherein each chain has a heterologous C-terminal dimerisation peptide which is a coiled coil domain (such as a leucine zipper from c-fos and c-jun) dimerization peptide, which dimerize, one with the other, and wherein a short flexible linker is between the TCR and the dimerisation domain, and further, wherein a disulfide bond present in the native TCR between the α and β chains adjacent to the cytoplasmic domain is absent from the recombinant TCR. WO 97/35991 does not teach the TCR complex of instant claims, wherein the disulfide bond between the α and β chain of the TCR are absent.

Golden et al teach soluble heterodimeric TCR comprising an α and β chain, each chain comprising a leucine zipper which dimerizes, one with the other, produced in *E. coli* at yields of 4-5 mg/L (especially Abstract).

O'Shea et al teach heterodimer formation through leucine zippers from c-fos and c-jun (especially Abstract).

Garbozci et al teach a soluble TCR without the interchain disulfide bond present in native TCRs, and that the heterodimerization, refolding and antigenic specificity of the TCR do not require its interchain disulfide bond, transmembrane segments or glycosylation (especially Abstract and page 5408, column 1). Garbozci et al further teach that when α and β chains expressed without the cysteines that form the interchain disulfide bond were refolded together, they formed heterodimers spontaneously and at higher yields. Garbozci et al teach the yield is routinely 100 mg/ml and the refolded noncovalently associated TCR is stable and very soluble and displays little or no aggegration upon long term storage at 4 degrees C (especially page 5404, column 1, lines 1-14 and page 5407, column 1 at lines 19-22). Garbozci et al teach that their methodology may be of general utility in refolding of other TCRs, since the sequences of αβ TCR are highly homologous and are expected to have essentially the same structure (especially paragraph spanning columns 1 and 2 on page 5409).

Schatz teaches a biotin holoenzyme synthetase encoded by birA, useful for labeling, purification, detection and immobilization of proteins. Schatz teaches fusion proteins comprising polypeptides and the birA sequence for biotinylation at a single specific site (especially abstract and last 2 paragraphs). Schatz teaches biotinylation of a variety of molecules is of practical importance, primarily due to the very tight binding of biotin to the proteins avidin and streptavidin, and that it is advantageous to accomplish biotinylation at a single site using an agent with site specificity (especially paragraph spanning columns 1 and 2 on page 1138).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have substituted the soluble heterodimeric TCR of Golden et al with addition of the Gly-Ser linker of WO 97/35991 as the monomeric TCR in the multimers of WO 97/35991 that were mulitmerized by avidin and to have produced the proteins in *E. coli* as taught by Golden et al. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made to have used any leucine zipper of appropriate stability such as the leucine zippers from c-fos and c-jun taught by O'Shea et al in the soluble heterodimeric TCR of Golden et al. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have to have a recombinant TCR as taught by the combination of WO 97/35991 and Golden et al without the disulfide bond, as taught by Garboczi et al and further modified as taught by Schatz with birA.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to increase the yield of correctly folded soluble TCR of WO 97/35991 as modified with leucine zippers as taught by Golden et al and O'Shea et al. One of ordinary skill in the art at the time the invention was made would have been motivated to do this because Garboczi et al teach that the presence of said bond is not important for heterodimerization and refolding, and further in order to facilitate the production of soluble correctly associated TCR, i.e., in order to insure that disulfide bonds did not form between homologous chains or with other contaminating proteins during purification.

With regard to instant claims 9 and 18, one of ordinary skill in the art at the time the invention was made would have been aware that biotin is the binding partner for avidin, and that biotin would have been incorporated into the monomer TCR in order that the monomer TCR could have been linked via avidin to form multimers and as taught by Schatz. With regard to instant claim 18, one of ordinary skill in the art at the time the invention was made would have been aware that the C-terminus of the heterodimer chain would be the optimal location for biotinylation, rather than at the N-terminus where preservation of antigen binding function was paramount.

Applicant's arguments in the amendment filed 4/15/05 have been fully considered, but are not persuasive.

It is Applicant's position is of record in the said amendment on pages 8-10, and is based on an assertion that: (1) since WO 97/35991 and Golden et al disclose only TCR that do have an interchain disulfide bond, there is no motivation in any of the references to omit the disulfide bond, (2) Garbozci et al do not teach or suggest any need for modification of the TCR chains to supplement, stabilize or encourage interchain heterodimerization in any way, (3) the omission of the disulfide bond only worked for Garboczi et al in the specific background of the precise TCR and concentration conditions employed by those authors, (4) that O'Shea does not teach whether the association between c-jun and c-fos would occur if these sequences were fused to TCR chains, nor whether any association would result in a functional TCR, (5) Applicant has presented arguments previously to why Garbozci et al does not support the weight of interpretation put upon it by the Examiner. In addition, Applicant argues the references separately.

It is the Examiner's position that one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success because: (1) WO 97/35991 and Golden et al are being argued separately from the other references by Applicant, (2) Garbozci et al do teach that when α and β chains expressed without the cysteines that form the interchain disulfide bond were refolded together, they formed heterodimers spontaneously and at higher yields. Garbozci et al teach the yield is routinely 100 mg/ml and the refolded noncovalently associated TCR is stable and very soluble and displays little or no aggegration upon long term storage at 4 degrees C as enunciated supra in this rejection, and that the yields are 100x to 20x higher than that taught by WO 97/35991 and Golden et al respectively, thus providing motivation to omit the disulfide bond, (3) Garbozci et al teach that their methodology may be of general utility in refolding of other TCRs since the sequences of αβ TCR are highly homologous and are expected to have essentially the same structure, and there is no recitation of a particular TCR or concentration conditions in the instant claims, (4) Golden et al teach properly folded soluble heterodimeric TCR comprising an α and β chain, each chain comprising a leucine zipper which dimerizes one with the other, and O'Shea et al teach leucine zippers from c-fos and c-jun that heterodimerize with each other, (5) the Examiner's position with respect to Applicant's previous arguments to Garbozci et al are of record.

Applicant is reminded that in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

6. Claims 24 and 25 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/35991 (Applicant's IDS reference in the Form 1449 filed 1/31/00) in view of Golden et al (J. Immunol. Meth., Vol. 206: 163-169, 1997, Applicant's IDS reference in the Form 1449 filed 11/5/99), O'Shea et al (Science, Vol. 245: 646-648, 1989, Applicant's IDS reference in the Form 1449 filed 11/5/99), Garboczi et al (J. Immunology, Volume 157: 5403-5410, 1996, Applicant's IDS reference in the Form 1449 filed 11/5/99) and Schatz (Biotechnology, 11, 1993, pages 1138-1143, Applicant's IDS reference in the Form 1449 filed 11/5/99) as applied to claims 1-11, 14-18, 26, 27 and 34-36 supra and further in view of U.S. Patent No. 5,635,363 (Applicant's IDS reference in Form 1449 filed 11/5/99).

WO 97/35991, Golden et al, O'Shea et al, Garboczi et al and Schatz (i.e., "the combined references") have been discussed supra. In addition, WO 97/35991 teaches that the multimeric soluble TCR complexes may be useful in defining the specific peptide/MHC ligands recognized by uncharacterized tumor-specific T cells and T cells involved in autoimmune responses (especially page 10, lines 27-31 and page 11, line 1).

The combined references do not teach a multimeric TCR complex comprising a "detectable label" recited in instant claim 25, nor attached to a solid structure" recited in instant claim 24.

U.S. Patent No. 5,635,363 discloses soluble MHC/peptide tetramers which are biotinylated and multimerized with streptavidin or with avidin and which further comprise a light detectable label FITC or an enzyme (especially claims) and which further may be bound to an insoluble support such as a bead, i.e., a "solid structure", for the purpose of assay (especially column 8, lines 4-16).

It would have been prima facie obvious to one of ordinary skill at the time the invention was made to have biotinylated, as disclosed by the '363 patent for soluble MHC/peptide tetramers, the soluble TCR complexes taught by the combined references and to have multimerized them using avidin, and further to have labeled them with a detectable label such as is disclosed by the '363 patent for the MHC/peptide tetramers, or to have bound them to a bead, i.e., a solid structure.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to form more avid multimers because the combined references teach the claimed TCR complexes, WO 97/35991 teaches multimers and tetramers and both WO 97/35991 and the '363 patent teach use of avidin for multimerization of heterodimeric proteins, and also because one of ordinary skill in the art at the time the invention was made would have been motivated to facilitate detection because WO 97/35991 teaches that multimeric soluble TCR complexes may be useful in defining the specific peptide/MHC ligands recognized by uncharacterized tumor-specific T cells and T cells involved in autoimmune responses.

Applicant's arguments of record in the amendment filed 4/15/05 on page 10 at "(ii)" have been fully considered, but are not persuasive.

Applicant's arguments and Examiner's position supra with regard to item #5 of this Office Action, apply herein.

7. Claims 1 and 19-24 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/35991 (Applicant's IDS reference in the Form 1449 filed 1/31/00) in view of Golden et al (J. Immunol. Meth., Vol. 206: 163-169, 1997, Applicant's IDS reference in the Form 1449 filed 11/5/99), O'Shea et al (Science, Vol. 245: 646-648, 1989, Applicant's IDS reference in the Form 1449 filed 11/5/99) and Garboczi et al (J. Immunology, Volume 157: 5403-5410, 1996, Applicant's IDS reference in the Form 1449 filed 11/5/99) and further in view of Ahmad et al (Cancer Res., Volume 53: 1484-1488, 1993).

WO 97/35991, Golden et al, O'Shea et al and Garboczi et al (i.e., "the combined references") have been discussed supra. The combined references do not teach a multimeric TCR complex attached to a lipid vesicle via derivatised lipid components of the vesicle.

Ahmad et al teach attachment of a biotinylated targeting antibody attached to the surface of a liposome containing biotinylated phosphatidylethanolamine by means of an avidin linker (especially Introduction and Liposome Preparation on page 1484). Ahmad et al further teach that liposomes containing lipid derivatives of polyethylene glycol have circulation times sufficiently long to allow for effective in vivo drug delivery.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have attached the multimeric TCR complex taught by the combined references to the liposome of Ahmad et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to effectively deliver *in vivo* the multimeric TCR complex taught by the combined references, including WO 97/35991 to be useful for *in vivo* therapy. Claim 23 is included in this rejection because it would also have been prima facie obvious to embed the TCR complex in the liposome of Ahmad et al because Ahmad et al teach effective delivery of a substance embedded in the liposome rather than attached to the surface via a derivatized component of the liposome (especially Abstract). Instant claim 24 is included in this rejection because the claim limitation "solid structure" can read on "liposome" of the art reference.

Applicant's arguments of record in the amendment filed 4/15/05 on pages 10-11 at "(iii)" have been fully considered, but are not persuasive.

Applicant's arguments and Examiner's position supra with regard to item #5 of this Office Action, apply herein.

8. Claims 1-11, 14-18, 24-27, and 34-36 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al (PNAS USA 1994, 91: 11408-11412, IDS reference) in view of Gregoire et al (PNAS USA 1991, 88: 8077-8081), Garboczi et al (J. Immunology, Volume 157: 5403-5410, 1996, Applicant's IDS reference in the Form 1449 filed 11/5/99), Wulfing (J. Mol. Biol. 1994, 242: 655-669), U.S. Patent No. 5,643,731 and U.S. Patent No. 5,582,996.

Chang et al teach a soluble TCR in which the TCR alpha and beta V and C extracellular segments are fused at the carboxy terminal end to 30 amino acid long segments via a cleavable flexible linker (Abstract and figure 2). Chang et al teach that the peptide segments have been previously shown to selectively associate to form stable heterodimeric coiled coil, the leucine zipper (Abstract and page 11408 at the second column, first three lines of the second paragraph). Chang et al teach that the disulfide linked αβ heterodimer is the clonally unique component that possesses a recognition site for antigen in the context of the MHC (page 11408, at the first column, first paragraph after Abstract). Chang et al teach that the structure of the heterodimeric TCR protein is judged to be native when probed with a panel of 17 mAbs specific for the alpha and beta C and V domains (Abstract and page 11411 at eh last paragraph bridging the page with page 11412). Chang et al further teach facilitation of association of any type of naturally occurring heterodimeric structure, and that association between individual protein domains, such as TCR Vα and Vβ can be fostered in the absence of other protein segments (Cα and Cβ) (page 11412, at the second column).

Chang et al do not teach that a disulfide bond present in native TCRs between the alpha and beta chain is absent in the recombinant TCR having both the alpha and beta variable and constant region domains, nor do Chang et al teach that the heterodimers are present as multivalent TCR complexes.

Gregoire et al teach multimers of chimeric soluble TCR- αβ heterodimers linked to Ig Cκ or to Ig CH_1, CH_2 or CH_3 (last paragraph on page 8081). Gregoire et al teach that the alpha chain consists of the TCR Vα region joined to the first exon of TCR Cα and the C region of the Igκ light chain, and the beta chain consists of the TCR Vβ region joined to the first exon of TCR Vβ and the C region of the Igκ light chain and the constructs expressed in *E. coli* (page 8078, second column at the last paragraph, figure 1 and figure 4 and Materials and Methods section). Gregoire et al teach that for multimers, one of the Igκ regions is replaced with Ig CH_1, CH_2 or CH_3 (last paragraph on page 8081). Gregoire et al teach that the chimeric polypeptides do not include the second exon of TCR Cα and Cβ gene, and therefore lack the cysteine residues normally involved in the covalent linkage of the TCRα and TCRβ chains (page 8080, first column at lines 2-6). Gregoire et al teach that the ability of their constructs to form heterodimers may be due to the lack of the cysteine residue located at the COOH-terminal to the Cα and Cβ regions (page 8080 at the second column, first paragraph). Gregoire et al teach that an illegitimate interaction between the COOH terminus of a TCR C domain and the

NH2 terminus of a Cκ domain may distort the proper pairing of the Cκ domains and accordingly their ability to be disulfide linked, i.e., the Cκ domains dimerize with each other, and that they associated as noncovalent dimers (page 8080 at the first column and last 8 lines bridging second column and page 8081, last paragraph, first sentence). Gregoire et al teach their TCR in a pharmaceutically acceptable formulation (page 8078, second column at the third full paragraph). With regard to the recitation of refolded recombinant TCR in claims 1 and 11, Gregoire et al teach 3 mAb epitopes on Vα and Vβ that are recognized on both their constructs as well as surface expressed TCR, that their constructs react with an anti-clonotypic antibody and two antibodies directed to the C domain of the TCR α and β chains, and that the soluble TCR molecules are folded in a conformation indistinguishable from that which they assume at the cell surface (Abstract and page 8081, first paragraph).

It is clear from figure 2 on page 11410 in the teaching of Chang et al, and from the teaching of Gregoire et al that without the C domains, a conjugate of TCR Vα and Vβ taught by Chang et al would not have the interchain disulfide bond because the cysteines that form the interchain disulfide is not found in the TCR Vα and Vβ. Furthermore, from the teaching of Gregoire et al, one of ordinary skill in the art would have expected that the lack of the disulfide bond located at the COOH terminal end of the Cα and Cβ regions facilitates the pairing of the dimerizing Ig Cκ or CH.

Garbozci et al teach a soluble TCR without the interchain disulfide bond present in native TCRs, and that the heterodimerization, refolding and antigenic specificity of the TCR do not require its interchain disulfide bond, transmembrane segments or glycosylation (especially Abstract and page 5408, column 1). Garbozci et al further teach that when α and β chains expressed without the cysteines that form the interchain disulfide bond were refolded together, they formed heterodimers spontaneously and at higher yields. Garbozci et al teach the yield is routinely 100 mg/ml and the refolded noncovalently associated TCR is stable and very soluble and displays little or no aggegration upon long term storage at 4 degrees C and binds specifically to the ligand HLA-A2/Tax (especially page 5404, column 1, lines 1-14, page 5406, second column at the last two paragraphs and page 5407, column 1 at lines 19-22).

Wulfing et al teach that the TCR fragments are correctly folded in the periplasm of *E. coli*. Wulfing et al teach that the correctly folded TCR is essentially stable, whereas misfolded TCR is rapidly degraded, and that the effect of increased yields in the direct over-expression system is due to enhanced in vivo folding, working synergistically with substantially higher intrinisic proteolytic stability of the correctly folded material (page 665, second column at the last two paragraphs, and that bridging page 666). Wulfing et al teach that to overcome the low affinity of TCR, T cells simultaneously use multiple TCRs to increase the avidity of recognition (last paragraph on page 795).

From the teaching of Wulfing et al, one of ordinary skill in the art at the time the invention was made would have expected that higher yields of TCRs are correlated with correct TCR folding, and thus a decrease in the yield of alpha and beta chains of TCR expressed with the interchain disulfide bonds, as compared to alpha and beta chains of TCR expressed without the interchain disulfide bonds as taught by Garboczi et al, indicates an increase in misfolding of alpha and beta chains of TCR expressed with the interchain disulfide bonds, i.e., that the interchain disulfide bond appears to interfere with the folding of the alpha and beta chains of TCRs.

Therefore, from the teaching of Garboczi et al and Wulfing et al, one of ordinary skill in the art at the time the invention was made would have expected that the interchain disulfide bond of TCR not only is not necessary for TCR binding to the target peptide, but that it could also interfere with the folding of the alpha and beta chains, resulting in lower yield.

U.S. Patent No. 5,643,731 discloses that c-jun and v-fos are particularly the preferred leucine zipper peptides (column3 at lines 38-42). U.S. Patent No. 5,643,731 further discloses that the leucine zipper peptides can be linked via a flexible linker to antigen receptor molecules, i.e., such as TCR or antibody, and multimerized via a carrier molecule that is a multivalent attachment molecule, and further that the constructs can be attached to solid supports (especially Abstract and Figures). U.S. Patent No. 5,643,731 discloses that the antigen receptor molecule-leucine zipper peptides can comprise a detectable label or a cytokine, i.e., an immunostimulating agent or enymes, i.e., protein tags, or other fusion proteins and also to streptavidin or biotin (especially Figures and column 4 at lines 30-36 and column 2).

U.S. Patent No. 5,582,996 discloses that dimeric Fab is formed when a Fab with a c-fos leucine zipper is mixed with a Fab with a c-jun leucine zipper. U.S. Patent No. 5,582,996 further discloses that the hinge region of the dimeric Fab retains sufficient flexibility to permit the Fab fragments to bind antigen in a manner similar to that of normal antibodies (especially Example 7 at columns 15-16).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have: combined the teaching of Chang et al that the association between individual protein domains such as TCR Vα and Vβ can be fostered in the absence of protein segments such as Cα and Cβ and use of coil coiled domains such as those that form leucine zippers linked to the said Vα and Vβ via linkers, the teaching of Gregoire et al that lack of the of the disulfide bond located at the COOH terminal end of Cα and Cβ facilitates pairing of the dimerizing construct and that multivalency is advantageous, the teaching of Garboczi et al that the interchain disulfide bond of TCR is not necessary for its binding to the target peptide/MHC and that it can interfere with folding of the alpha and beta chains, thus resulting in lower yield, the latter also taught by Wulfing et al, for making a chimeric TCR taught by Chang et al, wherein the interchain disulfide bond between the alpha and beta chains is omitted and to have

multimerized the soluble heterodimers for increased valency as taught by Gregoire et al and because Wulfing et al teach low affinity of TCR and need to increase the avidity for recognition using multiple TCRs (for cell surface TCR heterodimers), including as dimers, trimers or tetramers, in light of the disclosure of U.S. Patent No. 5,582,996 that leucine zipper peptides linked via a flexible linker to antigen receptor molecules can be multimerized via a carrier molecule that is a multivalent attachment molecule and/or can be linked to solid supports and in light of the disclosure of U.S. Patent No. 5,582,996 that c-jun and v-fos are particularly the preferred leucine zipper peptides and that of U.S. Patent No. 5,582,996 that a dimeric antigen receptor molecule is formed when a component of said molecule with a c-fos leucine zipper is mixed with another component with a c-jun leucine zipper. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have coupled or fused the construct to a solid support, or to a cytokine or to an enzyme or to biotin as disclosed for the antigen receptor molecule multimers disclosed by U.S. Patent No. 5,643,731. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have included the multimer in a composition with a pharmaceutically acceptable carrier since their TCR in a pharmaceutically acceptable formulation since Gregoire et al teach their TCR in a pharmaceutical composition. It would have been obvious to biotinylate the TCR complexes at the C-terminus because one of ordinary skill in the art would have expected that the C-terminus is not the site where the recognition of antigen takes place and would be least likely to interfere with antigen binding as compared to biotinylation at the N-terminus.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a multimeric TCR complex of higher avidity and in higher yield, as per the teachings of the references as enunciated herein.

With regard to instant claim 17, the recitation of a method wherein the claimed product is made carries no patentable weight in these product claims.

Applicant's arguments of record in the amendment filed 4/15/05 on pages 11-14 at "(iv)" have been fully considered, but are not persuasive.

It is the Examiner's position that regardless of why the portion of each TCR Cα and Cβ domain encoded by exon 2 should be deleted in the construct taught by Gregoire et al, the teaching of Gregoire et al that the unique ability of their construct to form alpha-κ-beta-κ dimers may be due to the lack of the cysteine residue located at the carboxy terminal end of the Cα and Cβ regions (page 8080 at the second column, first paragraph) clearly indicates that the lack of disulfide bond located at the C terminal end of the Cα and Cβ regions facilitates the dimerization process of the dimerizing domains, i.e., the cysteine residue located at the carboxy terminal end of the TCR is a hindrance in the dimerization process. Furthermore, although Gregoire et al is published in 1991 and was available to Chang et al, and although Chang et al did not attempt to make the construct without an interchain disulfide bond, it is noted that this defect is cured by the

teaching of Garboczi et al. In addition, Chang et al is relied upon to show that the leucine zipper is an effective and preferred dimerizing domain for TCR. A cited reference does not have to teach all aspects of the claimed invention. It is the Examiner's further position that Wulfing et al is relied upon for the general teaching that correctly folded TCR is stable, whereas misfolded TCR is rapidly degraded, and that increased yield is due to enhanced *in vivo* folding working in synergy with substantially higher intrinsic proteolytic stability of the correctly folded material. From the teaching of Wulfing et al one of ordinary skill in the art at the time the invention was made would have expected that higher yields of TCR is correlated with correct TCR folding, and a decrease in the yield of alpha and beta chains of TCR expressed with the interchain disulfide bonds, as compared to the alpha and beta chains of TCR expressed without the interchain bonds as taught by Garboczi et al indicates an increase in misfolding of alpha and beta chains of TCR expressed with the interchain disulfide bond. Thus, from the teaching of Garboczi et al and Wulfing et al, one of ordinary skill in the art would have expected that the interchain disulfide bond of TCR not only is not necessary for TCR function, but also interferes with folding of the alpha and beta chains, resulting in lower yields. With regard to Applicant's previous arguments to Garboczi et al, the Examiner's position is of record in the previous office actions. Applicant argues the '731 and '996 patents separately. Applicant is reminded that in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

9. Claims 19-23 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al (PNAS USA 1994, 91: 11408-11412, IDS reference) in view of Gregoire et al (PNAS USA 1991, 88: 8077-8081), Garboczi et al (J. Immunology, Volume 157: 5403-5410, 1996, Applicant's IDS reference in the Form 1449 filed 11/5/99), Wulfing (J. Mol. Biol. 1994, 242: 655-669), U.S. Patent No. 5,643,731 and U.S. Patent No. 5,582,996 as applied to claims 1-11, 14-18, 24-27, and 34-36 above, and further in view of Ahmad et al (Cancer Res. 1993, 53: 1484-1488, of record).

The teaching of Chang et al, Gregoire et al, Garboczi et al, Wulfing et al, U.S. Patent No. 5,643,731 and U.S. Patent No. 5,582,996 have been set forth above, hereafter "the combined references".

The combined references do not teach wherein the multimeric TCR complex is attached to a lipid vesicle via derivatized lipid components of the vesicle.

Ahmad et al teach attachment of a biotinylated targeting antibody attached to the surface of a liposome containing biotinylated phosphatidylethanolamine by means of an avidin linker (especially Introduction and Liposome Preparation on page 1484). Ahmad et al further teach that liposomes containing lipid derivatives of polyethylene glycol have circulation times sufficiently long to allow for effective in vivo drug delivery.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have attached the multimeric TCR complex taught by the combined references to the liposome of Ahmad et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to effectively deliver in vivo the multimeric TCR complex taught by the combined references, to be useful for in vivo administration, since Ahmad et al teach enhancement of in vivo delivery an antigen receptor using liposomes and Gregoire et al teach pharmaceutical compositions comprising another antigen receptor, TCR. Claim 23 is included in this rejection because it would also have been prima facie obvious to embed the TCR complex in the liposome of Ahmad et al because Ahmad et al teach effective delivery of a substance embedded in the liposome rather than attached to the surface via a derivatized component of the liposome (especially Abstract). Instant claim 24 is also included in this rejection because the claim limitation "solid structure" can read on "liposome" of the art reference.

Applicant's arguments of record in the amendment filed 4/15/05 on page 14 at "(v)" have been fully considered, but are not persuasive.

Applicant's arguments and Examiner's position supra with regard to item #8 of this Office Action, apply herein.

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 1-11, 14-27 and 34-36 stand provisionally rejected under the judicially created doctrine of double patenting over claims 22-34 of copending Application No. 10/014,326 in view of WO 97/35991, Ahmad et al and U.S. Patent No. 5,643,731. This is a provisional double patenting rejection.

The instant claims are drawn to a multivalent TCR, whereas the claims of Application No. 10/014,326 are drawn to a heterodimeric monovalent TCR.

WO 97/35991 teaches soluble (i.e., extracellular domains) recombinant divalent and multivalent analogs (including tetravalent, i.e., a tetramer) of heterodimeric proteins and pharmaceutical compositions thereof, including αβ TCR that possess enhanced affinity for their target molecules, said αβ TCRs being associated via Ig linker molecules which may further comprise a toxin, i.e., a "cytotoxic agent" as recited in instant claim 26, and/or may be further linked by association via avidin (especially page 8, line 31, page 9, lines 1-4, page 10, lines 27-31, page 11, lines 1-7, page 14, lines 7-16, Figure 1D and legend, claims 1-5, 8, 10-14, 17, 27 and 28, page 1, lines 14-17, page 16, lines 1-14). In addition, WO 97/35991 teaches that the multimeric soluble TCR complexes may be useful in defining the specific peptide/MHC ligands recognized by uncharacterized tumor-specific T cells and T cells involved in autoimmune responses (especially page 10, lines 27-31 and page 11, line 1). WO 97/35991 also teaches production of the multimers in baculovirus with a yield of about 1 ug/ml (i.e., about 1 mg/L). WO 97/35991 also teaches short flexible Gly-Ser spacers between the TCR chain and the Ig portion (Figure 1D and legend).

Ahmad et al teach attachment of a biotinylated targeting antibody attached to the surface of a liposome containing biotinylated phosphatidylethanolamine by means of an avidin linker (especially Introduction and Liposome Preparation on page 1484). Ahmad et al further teach that liposomes containing lipid derivatives of polyethylene glycol have circulation times sufficiently long to allow for effective in vivo drug delivery.

U.S. Patent No. 5,643,731 discloses that c-jun and v-fos are particularly the preferred leucine zipper peptides (column3 at lines 38-42). U.S. Patent No. 5,643,731 further discloses that the leucine zipper peptides can be linked via a flexible linker to antigen receptor molecules, i.e., such as TCR or antibody, and multimerized via a carrier molecule that is a multivalent attachment molecule, and further that the constructs can be attached to solid supports (especially Abstract and Figures). U.S. Patent No. 5,643,731 discloses that the antigen receptor molecule-leucine zipper peptides can comprise a detectable label or a cytokine, i.e., an immunostimulating agent or enymes, i.e., protein tags, or other fusion proteins and also to streptavidin or biotin (especially Figures and column 4 at lines 30-36 and column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have constructed multimers of the heterodimeric monovalent TCR of Application No. 10/014,326 given the teaching of WO 97/35991 and U.S. Patent No. 5,643,731 and to have attached the multimeric TCR complexes to the liposome taught by Ahmad et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to construct higher avidity TCR/composition thereof comprising a pharmaceutically acceptable formulation because WO 97/35991 teaches TCR multimers have enhanced affinity and Ahmad et al teach enhanced in vivo drug delivery for another type of antigen receptor using liposomes and U.S. Patent No. 5,643,731 discloses heterodimerized αor β TCR chains with leucine zippers, and attachment to labels or cytokines or biotin or streptavidin. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to effectively deliver the multimeric TCR complex in vivo. Instant claim 23 is included in this rejection because it would also have been prima facie obvious to embed the TCR complex in the liposome because Ahmad et al teach effective delivery of a substance embedded in the liposome rather than attached to the surface via a derivatized component of the liposome.

Instant claim 24 is included in this rejection because the claim limitation "solid structure" can read upon liposome. With regard to the recitation of "therapeutic agent" in claim 33 of Application No. 10/014,326, claim 26 of the instant application recites "cytotoxic agent or an immunostimulating agent", i.e., a "therapeutic agent". Although instant claim 8 recites "fusion protein comprising an amino acid sequence encoding a protein tag", the teaching of WO 97/35991 is for a toxin, that toxin potentially being a protein. Claims 23-25 of Application No. 10/014,326 recite wherein said TCR is stable at low concentrations, a concentration of about 20 mg/ml, or a concentration below 1 mg/ml, respectively. Although the references do not teach the TCR is stable at the recited concentrations, the claimed multimeric TCR appears to be the same as that recited in claims 23-25 of Application No. 10/014,326. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of Application No. 10/014,326 does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on Applicant to prove that the claimed product is different from that recited in Application No. 10/014,326 and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977).

Applicant's arguments in the amendment filed 4/15/05 to hold the instant rejection in abeyance until such time as the Examiner indicates allowable subject matter has been fully considered, but is not persuasive.

The Examiner is required to maintain the instant rejection.

In view of Applicant's amendment filed 4/15/05, the following are new grounds of rejection.

12. For the purpose of prior art rejections, the filing date of the instant claims 1-11, 14-27 and 34-36 is deemed to be the filing date of PCT/GB99/01583, i.e. 5/19/99, as certified copies of the foreign priority applications have not been received.

13. Claims 1-11, 14-18, 25-27, and 34-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pecorini et al (JMB 285(4) 1/29/99, Applicant's newly submitted IDS reference in Applicant's PTOL-1449 filed 1/25/05) in view of Gregoire et al (PNAS USA 1991, 88: 8077-8081), Wulfing (J. Mol. Biol. 1994, 242: 655-669) and U.S. Patent No. 5,643,731.

Pecorini et al teach high yield production of a functional and soluble αβ TCR with the intermolecular Cα-Cβ disulfide bridge deleted, said disulfide bridge responsible for aggregation during folding. Pecorini et al further teach the said αβ TCR wherein each chain is fused to c-jun or c-fos leucine zipper heterodimerization domains (especially abstract and page 1837 at full paragraph at column 2).

Pecorini et al do not teach wherein the TCR are multimerized, i.e., have increased binding ability, including linked via a flexible linker and multimerized via a carrier molecule that is a multivalent attachment molecule, nor further that the constructs can be attached to solid supports, nor that they comprise a detectable label or a cytokine, i.e., an immunostimulating agent or enymes, i.e., protein tags, or other fusion proteins and also to streptavidin or biotin.

Gregoire et al teach multimers of chimeric soluble TCR- αβ heterodimers linked to Ig Cκ or to Ig CH_1, CH_2 or CH_3 (last paragraph on page 8081). Gregoire et al teach that the alpha chain consists of the TCR Vα region joined to the first exon of TCR Cα and the C region of the Igκ light chain, and the beta chain consists of the TCR Vβ region joined to the first exon of TCR Vβ and the C region of the Igκ light chain and the constructs expressed in *E. coli* (page 8078, second column at the last paragraph, figure 1 and figure 4 and Materials and Methods section). Gregoire et al teach that for multimers, one of the Igκ regions is replaced with Ig CH_1, CH_2 or CH_3 (last paragraph on page 8081). Gregoire et al teach that the chimeric polypeptides do not include the second exon of TCR Cα and Cβ gene, and therefore lack the cysteine residues normally involved in the covalent linkage of the TCRα and TCRβ chains (page 8080, first column at lines 2-6). Gregoire et al teach that the ability of their constructs to form heterodimers may be due to the lack of the cysteine residue located at the COOH-terminal to the Cα and Cβ regions (page 8080 at the second column, first paragraph). Gregoire et al teach that an illegitimate interaction between the COOH terminus of a TCR C domain and the NH2 terminus of a Cκ domain may distort the proper pairing of the Cκ domains and accordingly their ability to be disulfide linked, i.e., the Cκ domains dimerize with each

other, and that they associated as noncovalent dimers (page 8080 at the first column and last 8 lines bridging second column and page 8081, last paragraph, first sentence). Gregoire et al teach their TCR in a pharmaceutically acceptable formulation (page 8078, second column at the third full paragraph). With regard to the recitation of refolded recombinant TCR in claims 1 and 11, Gregoire et al teach 3 mAb epitopes on Vα and Vβ that are recognized on both their constructs as well as surface expressed TCR, that their constructs react with an anti-clonotypic antibody and two antibodies directed to the C domain of the TCR α and β chains, and that the soluble TCR molecules are folded in a conformation indistinguishable from that which they assume at the cell surface (Abstract and page 8081, first paragraph).

Wulfing et al teach that the TCR fragments are correctly folded in the periplasm of *E. coli*. Wulfing et al teach that the correctly folded TCR is essentially stable, whereas misfolded TCR is rapidly degraded, and that the effect of increased yields in the direct over-expression system is due to enhanced in vivo folding, working synergistically with substantially higher intrinisic proteolytic stability of the correctly folded material (page 665, second column at the last two paragraphs, and that bridging page 666). Wulfing et al teach that to overcome the low affinity of TCR, T cells simultaneously use multiple TCRs to increase the avidity of recognition (last paragraph on page 795).

U.S. Patent No. 5,643,731 discloses that c-jun and v-fos are particularly the preferred leucine zipper peptides (column3 at lines 38-42). U.S. Patent No. 5,643,731 further discloses that the leucine zipper peptides can be linked via a flexible linker to antigen receptor molecules, i.e., such as TCR or antibody, and multimerized via a carrier molecule that is a multivalent attachment molecule, and further that the constructs can be attached to solid supports (especially Abstract and Figures). U.S. Patent No. 5,643,731 discloses that the antigen receptor molecule-leucine zipper peptides can comprise a detectable label or a cytokine, i.e., an immunostimulating agent or enymes, i.e., protein tags, or other fusion proteins and also to streptavidin or biotin. U.S. Patent No. 5,643,731 discloses using the complexes for in vitro diagnosis or immunochemical detection (especially Figures and column 4 at lines 30-36 and column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have increased avidity of low affinity TCR as taught by Wulfing et al by multimerizing the TCR taught by Pecorini et al as per the teaching of Gregoire et al and U.S. Patent No. 5,643,731, and to have linked via a flexible linker and to have multimerized via a carrier molecule that is a multivalent attachment molecule as disclosed by U.S. Patent No. 5,643,731, or to have attached the constructs to solid supports, or to design them to comprise a detectable label or a cytokine, i.e., an immunostimulating agent or enymes, i.e., protein tags, or other fusion proteins and also to streptavidin or biotin, as disclosed by U.S. Patent No. 5,643,731.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to increase the avidity of TCR recognition because Wulfing et al teach T cells simultaneously use multiple TCRs to increase the avidity of recognition since TCRs have low affinity, and Gregoire et al and U.S. Patent No. 5,643,731 teach multimerization of TCRs, and Patent No. 5,643,731 discloses the usefulness of such reagents linked or fused to carrier molecules, solid supports, labels, cytokines, enzymes, streptavidin or biotin.

14. Claims 19-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pecorini et al (JMB 285(4) 1/29/99, Applicant's newly submitted IDS reference in Applicant's PTOL-1449 filed 1/25/05) in view of Gregoire et al (PNAS USA 1991, 88: 8077-8081), Wulfing (J. Mol. Biol. 1994, 242: 655-669) and U.S. Patent No. 5,643,731 as applied to claims 1-11, 14-18, 25-27, and 34-36 above, and further in view of Ahmad et al (Cancer Res. 53: 1484-1488, 1993).

Pecorini et al, Gregoire et al, Wulfing and U.S. Patent No. 5,643,731 have all been discussed above, hereafter referred to as the "combined references".

The combined references do not teach wherein the multimeric TCR complex is attached to a lipid vesicle via derivatized lipid components of the vesicle.

Ahmad et al teach attachment of a biotinylated targeting antibody attached to the surface of a liposome containing biotinylated phosphatidylethanolamine by means of an avidin linker (especially Introduction and Liposome Preparation on page 1484). Ahmad et al further teach that liposomes containing lipid derivatives of polyethylene glycol have circulation times sufficiently long to allow for effective in vivo drug delivery.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have attached the multimeric TCR complex taught by the combined references to the liposome of Ahmad et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to effectively deliver *in vivo* the multimeric TCR complex taught by the combined references, to be useful for *in vivo* administration, since Ahmad et al teach enhancement of *in vivo* delivery an antigen receptor using liposomes and Gregoire et al teach pharmaceutical compositions comprising another antigen receptor, TCR. Claim 23 is included in this rejection because it would also have been prima facie obvious to embed the TCR complex in the liposome of Ahmad et al because Ahmad et al teach effective delivery of a substance embedded in the liposome rather than attached to the surface via a derivatized component of the liposome (especially Abstract). Instant claim 24 is also included in this rejection because the claim limitation "solid structure" can read on "liposome" of the art reference.

15. The references crossed out in the Form 1449 filed 14/25/05 have not been considered because a legible copy of each patent application or that portion which caused it to be listed; and all other information or that portion which caused it to be listed has not been provided to the Examiner. It is noted by the Examiner that the list of references cited in the international search report for PCT/US95/16937 has not been considered because it is not listed on the said Form 1449.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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